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Evaluating NGS Testing in HER2m NSCLC: Overcoming Barriers to Clinical Adoption

Announcer:
Welcome to Project Oncology on ReachMD, sponsored by AstraZeneca and Daiichi Sankyo. Here's your host, Dr. Jacob Sands

Dr. Sands:
This is *Project Oncolo*gy, and I'm Dr. Jacob Sands. Joining me to share insights on integrating next generation sequencing and identifying HER2 mutations in non-small cell lung cancer is Dr. Tejas Patil, Assistant Professor of Medicine in Medical Oncology at the University of Colorado Cancer Center. Dr. Patil, welcome to the program.

Dr. Patil:
Thank you for having me.

Dr. Sands:
So let's dive right in, Dr. Patil. What kind of role does next-gen sequencing play, specifically for patients with HER2-mutated non-small cell lung cancer?

Dr. Patil:
That's a great question. I would say that if we look at the NCCN guidelines, it's pretty clearly listed that patients with lung cancer, in general, should receive broad-based molecular testing. Now how that's exactly spelled out isn't laid out with high level of granularity, but I would say that most providers would utilize some form of next generation sequencing on any patient with lung cancer, and that's because HER2 exon 20 insertions and HER2 alterations – which is the term that I'm gonna use to incorporate both the exon 20 insertion but also more rarely, the gene amplifications and the fusions – are an increasingly important subset within non-small cell lung cancer, and there are clinical trials underway looking at targeted approaches to these mutations.

Dr. Sands:
And how does next generation sequencing compare to single gene assays? Of course, we see them with mutations such as EGFR, with fusions such as ALK. Where does HER2 fit within there as far as single gene testing for HER2 as opposed to the broader next generation sequencing?

Dr. Patil:
Yeah, excellent question. So there was a very nice publication by Josh Bauml in *Journal of Thoracic Oncology*, published in 2018, that looked at a very similar mutation to HER2 exon 20 insertion, and these are the EGFR exon 20 insertions. And what we found was that EGFR exon 20 is a very diverse subset of mutations, and it's very similar to HER2 in this regard, and that there are significant limitations to single gene assessments, specifically through PCR-based testing. And part of the challenge is that it's very difficult to design primers and probes to cover every possible alteration in this manner, and so what this study showed was that there was a significant number of EGFR exon 20 insertions that were missed by PCR, but subsequently found by next generation sequencing. And so, in general, if the tissue allows, I think next generation sequencing would be the more optimal strategy in order to expand coverage and depth of detecting these diverse subset mutations.

Dr. Sands:
And then a couple follow-ups to that. So with HER2 mutations, are there any comutations that one would potentially see? Is this one of those that stands alone? And then, is there any challenge with tissue as far as the amount of tissue being used in single gene testing and then when using next generation sequencing?

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Dr. Patil:
Right, so I will answer the first question about comutations in HER2-altered non-small cell lung cancer. So HER2 alterations in lung cancer account for approximately one to four percent of all cases of non-small cell lung cancer, disproportionately within lung adenocarcinomas. And there's really good data to suggest that HER2 alterations, as a primary driver, are largely mutually exclusive with other oncogene drivers, like EGFR, KRAS or ALK. In terms of whether they're comutations that affect prognosis, that has yet to be described in great detail. We know that among EGFR-positive non-small cell lung cancer, the presence of a TP53 mutation has been associated with the worst progression-free survival on EGFR TKIs, relative to the group of patients that do not harbor a TP53 alteration. We haven't done this kind of analysis yet with HER2-mutant non-small cell lung cancer, though as more and more studies emerge, this kind of prognostic analysis will become more and more common.

Now getting to the issue of samples, I'm gonna answer this question in two ways. One – there are sometimes logistical problems related to the anatomic site in which you are trying to biopsy. As providers, we are all familiar with the inherent risks of lung biopsies, which include pneumothorax, and it can be difficult to obtain large volumes of tissue from the lung given this known risk. And so very often, especially with lung and sometimes pleural disease, it can be difficult to get a complete specimen that can be used for next generation sequencing, but this is completely due to the anatomic realities of where this tumor is located. I will also mention that bone specimens present a particular challenge, because the decalcification process can sometimes render the DNA and RNA from those samples much less usable and can compromise the quality of the molecular testing needed. In terms of challenges from the test site, the biggest challenge that I notice is related to getting quality specimens so that we can run RNA-based NGS testing.

In general, RNA-based NGS testing is much more effective at determining gene fusions, such as ALK, ROS1 or RET, and is very useful for detecting MET exon 14 skip mutations, but the test can really only be done if the quality of the RNA is sufficient. And so that's a general test issue that can be something that we run into when we think about triaging different types of tissue for either DNA- or RNA-based NGS.

Dr. Sands:
So let me then ask: within your clinical practice, which of the patients with lung cancer are you testing? Who would you consider standard of care for doing next generation sequencing to look for HER2 and some of these other genomic alterations?

Dr. Patil:
So within my practice, I actually test every single patient with non-small cell lung cancer for oncogene drivers, and that's because there's a high percentage of patients with adenocarcinomas – roughly 45-50%, depending on the gene profile that you look at and the study that you also look at – will have some kind of oncogene driver that could be targetable. Now that number is smaller within squamous cell carcinoma, but it still is the case that we do see oncogene-driven squamous cell carcinomas, and the common oncogenes that we typically see in this population are MET exon 14 skip mutation, BRAF V600E, and EGFR although they typically tend to be either compound EGFR mutations or atypical EGFR mutations. But in any case, knowledge of any of these three oncogenes is relevant because it allows a patient with squamous cell carcinoma the option of a targeted approach, which would be really helpful given how challenging and sometimes chemo-refractory this patient population can be.

Dr. Sands:
For those just tuning in, you're listening to *Project Oncology* on ReachMD. I'm Dr. Jacob Sands, and I'm speaking with Dr. Tejas Patil about next generation sequencing and identifying HER2 mutations in non-small cell lung cancer.

So Dr. Patil, let's focus on some challenges with implementing NGS. What are some of the barriers to testing at the University of Colorado Cancer Center, as well as within the community setting? What are you seeing?

Dr. Patil:
I think the biggest barriers come from the following: One is that NGS testing, in my opinion, can be a much more efficient way to kind of in a quick manner, identify relevant oncogenes, as opposed to sort of piecemeal testing using PCR-based approaches. I think that piecemeal strategy made sense five to six years ago when ALK, EGFR, and ROS1 were really the only targetable oncogenes, and everything else was considered non-targetable with chemotherapy and/or chemoimmunotherapy being the only treatment options. I think that roster is rapidly changing, and now with the emergence of targetable KRAS G12C options, NGS really is the more efficient method to molecularly profile patients with lung cancer. There are some challenges with NGS. I think the big challenges tend to be that there are differences between DNA- and RNA-based NGS testing, and I will also mention that there should be caution exercised when seeing gene amplification reported through NGS platforms. I will just say that the methods for standardizing gene amplification vary across commercial assays and do not have the same level of research and rigor as FISH-based testing, especially when we're talking about HER2 amplification.

Dr. Sands:

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And transitioning now to the community setting, are there any challenges that you've heard about, and any ways of overcoming those?

Dr. Patil:
So the biggest challenge is that a lot of these commercial assays will require send-out molecular testing. And that adds time to the patient workup and adds some delays in terms of identifying the appropriate oncogene, if any. At Colorado, we are thankful to have in-house molecular testing, but that's not a reality for most physicians practicing in the community, and send-out tests are inevitable. I would say that in general, if possible, it is advisable to use circulating tumor DNA assays concurrently with tumor assays, just because especially with lung cancer and especially with lung or pleural biopsies, there can be a problem of getting a suboptimal specimen for molecular testing, and by doing blood-based circulating tumor DNA assays concurrently with tissue-based biopsies, you can significantly increase the yield of finding a driver oncogene, which can have major implications for therapy among our patients.

Dr. Sands:
So looking ahead, what do you see for next-gen sequencing testing, or just genomic testing in general for lung cancer looking forward?

Dr. Patil.
Great, so that's a wonderful question, and I see next generation sequencing having two roles moving forward. The first role will be to better understand how certain comutations adversely or favorably affect prognosis. I mentioned TP53 already, and there are robust data showing that patients with EGFR, ALK, non-small cell lung cancer who harbor TP53 mutations, do have a worse prognosis than patients who do not. Now that's just one example. Within the space of immunotherapy, there is increasing evidence that KEAP1 and STK11 mutations seem to be associated with worse outcomes to immune therapy. Now this is a correlational analysis. We don't quite understand how this is a causal reason for why they're associated with the worse immune therapy response. But these kind of analyses I think will become much more commonplace with the widespread use of next generation sequencing. The other major role for next generation sequencing is to really understand mechanisms of acquired resistance when patients are on targeted therapies, and I think it'll be very much within common practice to biopsy, either using circulating tumor assays or through tissue biopsy, patients that are progressing on targeted therapies to really dig deep and look for possible mechanisms of acquired resistance so that we can come up with rational, sequential, combinational strategies for these patients.

Dr. Sands:
Well with those forward-looking thoughts in mind, I want to thank my guest, Dr. Tejas Patil, for joining me to discuss next generation sequencing and identifying HER2 mutations in non-small cell lung cancer. Dr. Patil, pleasure having you on the program.

Dr. Patil:
Thank you very much. Appreciate chatting.

Announcer:
This was Project Oncology, sponsored by AstraZeneca and Daiichi-Sankyo. To access other episodes in this series, visit reachmd.com/ProjectOncology, where you can be part of the knowledge.

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